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S/N 09/182,645

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jia-He Li and Jie Zhang	Examiner:	Wang, Shengjun
Serial No.:	09/182,645	Group Art Unit:	1617
Filed:	October 30, 1998	Docket No.:	60014.0001US01
Title:	Pharmaceutical Compositions Containing Poly(ADP-Ribose) Glycohydrolase Inhibitors and Methods of Using Same		

CERTIFICATE UNDER 37 C.F.R. 1.10
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By: Shanda Clemmons
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APPELLANTS' BRIEF UNDER 37 C.F.R. § 1.192

BOX AF
Commissioner for Patents
Washington, D.C. 20231

Dear Commissioner:

A Notice of Appeal was filed in this application on March 1, 2002. This Brief, filed in triplicate, is filed with the requisite fees and Appendix.

I. Real Party in Interest

The real party in interest is Guilford Pharmaceuticals, Inc., the assignee of the present application.

II. Related Appeals and Interferences

The assignee, the assignee's legal representatives, and the appellants are unaware of any other appeals or interferences that will affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. Status of Claims

Claims 46-49 are pending in the present application. Original claims 1-25 have been withdrawn with traverse from consideration as being drawn to a nonelected invention. Original claims 28-31, and 35-38 have been withdrawn with traverse as being drawn to a nonelected species. Claims 26-27, 32-34, and 39-45 have been canceled.

IV. Status of Amendments

No amendments were filed after the Final Office Action.

V. Summary of Invention

The claimed invention is directed to a method for treating neural or cardiac tissue damage resulting from a disease or condition by administrating to a mammal in need thereof a therapeutically effective amount of an inhibitor of poly(ADP-ribose) glycohydrolase (known as "PARG"). (Specification, pg. 25, lines 10-25; pg. 32, lines 2-8, 19-24; pg. 68, lines 18-24; pg. 69, line 7 through pg. 70, line 7; pg. 71 lines 8-19; pg. 72 line 20 through pg. 73, line 17; claim 46.) The inventors have discovered that PARG inhibitors can be used to inhibit or decrease free radical induced cellular energy depletion, cell damage, or cell death, thereby allowing the

treatment of a disease or condition resulting from cell damage or death due to necrosis or apoptosis. (See, e.g., Specification, pg. 31, lines 6-10.)

In one embodiment of the invention, PARG inhibitors were discovered to treat cardiovascular tissue damage resulting from cardiac ischemia, reperfusion injury, cardiovascular disease, heart attack, and vascular stroke. (Specification, pg. 72 line 72 through pg. 73, line 17; pgs. 86-87, Example 2; pgs. 89-90, Examples 5-7.) In another embodiment, PARG inhibitors are used to treat neural tissue damage in a mammal resulting from cerebral ischemia, neurodegenerative disease, neurological disease, and head trauma. (Specification, pg. 73, lines 17-23; pgs. 84-86, Example 1.)

VI. Issues Presented on Appeal

The issues presented for this appeal are (1) whether claims 46-49 directed to a method of administrating PARG inhibitors to treat neural and cardiac tissue damage resulting from certain diseases and conditions are anticipated by Wang's sugar free ginseng tea (Patent no. 1077644A),[1] Ning's coffee-flavored ginseng tea (Patent no. 1113711A),[2] and Tanuma's AB (JP 3-205402)[3] or AC (JP 4-13684)[4] cancer treating PARG inhibiting lignin glycoside; and (2) whether claims 46-49 are rendered obvious by Wang or Ning in view of Tanuma AB and AC.

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[1] A true and accurate translation of Wang is attached as Exhibit ("Ex.") A.
[2] A true and accurate translation of Ning is attached as Exhibit B.
[3] A true and accurate translation of Tanuma AB is attached as Exhibit C.
[4] A true and accurate translation of Tanuma AC is attached as Exhibit D.

VII. Grouping of Claims

Claims 46-47 should be considered as a group.

Claims 48-49 should be considered as a group.

VIII. Argument

Appellants' claims are to methods of treating neural or cardiac tissue damage resulting from a disease or condition by administering to a mammal in need thereof a therapeutically effective amount of an inhibitor of poly(ADP-ribose) glycohydrolase ("PARG"). The Wang and Ning references cited by the Examiner in the Final Office Action do not disclose or suggest a *therapeutic treatment* for any disease, let alone for diabetes or ischemia. Neither do they disclose or suggest the other claim limitations, i.e., treating neural or cardiac tissue damage with a PARG inhibitor. When read in combination with Wang or Ning, the Tanuma references do not solve the noted deficiencies. The rejections of claims 46-49 should be reversed.

A. Claims 46-49 are not Anticipated by Wang, Ning, or Tanuma

In the Final Office Action dated December 3, 2001 ("Action"), claims 46-49 were rejected under 35 U.S.C. § 102(b) as being anticipated by Wang, Ning, and Tanuma (AB and AC). Specifically, the Examiner asserted that (1) Wang teaches a method of treatment of diabetes comprising administering ginseng to the patient, and (2) Ning teaches a method of treatment of ischemia comprising administering ginseng to the patient. The Examiner also noted that Tanuma teaches that ginseng hot water extract contains "the lignin glycoside herein. Therefore the claimed method herein read on the method taught by Wang and Ning." (Action, pgs. 2-3.)

Applicants respectfully submit that the Examiner has erroneously interpreted the Wang and Ning references. With respect to Wang, the Examiner reads this reference to disclose a treatment for diabetes. This is factually incorrect. Wang teaches a procedure for the production of a sugar free tea product. Because the tea product is sugar free, the consumption of such tea product is "suitable for diabetes patients." (Wang, Ex. A, pg. 1.) The sugar free tea product is suitable for diabetes patients not because it acts as a therapeutic that treats the underlying disease of diabetes, but rather because the product does not worsen an already known disease or condition. As Wang states "[t]he advantage of said product is that it contains no sugar and is suitable for ingestion by all people." (Wang, Ex. A, pgs. 1, 3).[5] The sugar free tea product disclosed in Wang is not a therapeutic agent that treats diabetes or any other disease or condition. Thus at least two elements of claim 46—therapeutic treatment of neural or cardiac tissue damage resulting from a disease or condition in a mammal—are plainly not described in Wang. The Examiner's rejection with respect to Wang is improper.

The Ning reference shares certain key disqualifying traits with Wang in that it describes "a nourishing health beverage of coffee-flavored ginseng tea." (Ning, Ex. B, pg. 1.) Similar to Wang, Ning extols the unsupported and mysterious "health protecting effects" of coffee-flavored ginseng tea. But again like Wang, Ning does not disclose the elements of claim 46, i.e., therapeutically treating neural or cardiac tissue damage resulting from a disease or condition. Rather, Ning teaches the following about its health beverage:

> This formula utilizes ginseng which supplements energy and promotes production of body fluid, stimulates central nerve system,

[5] Wang also mentions, without one word of explanation, that its sugar free tea product has "therapeutic and preventing effects." (Wang, Ex. A, pgs. 1, 3.) Such a generic, undefined, and unsupported claim does not provide any guidance to one of ordinary skill in the art who might consider the therapeutic usefulness of sugar free ginseng tea.

> reduces blood sugar and improves heart contraction and heart rate . . . .
>
> It can be used as a concentrate or beverage, combining medicine, health protecting effects and beverage in one and suitably applicable to middle-aged and elderly individuals experiencing prostration due to a long illness, neurasthenia, myocardial ischemia and cerebral and physical exhaustion.

(Ning, Ex. B, pgs. 1-2.)

Whatever one of skill in the art believes about these unsupported protective health effects of Ning's coffee-flavored ginseng tea, they do not describe a therapeutic treatment of neural or cardiac tissue damage resulting from a disease or condition as claimed in claims 46-49. Ning only teaches that a person who drinks coffee-flavored ginseng tea may temporarily receive certain body stimulating health effects. Coffee-flavored ginseng tea is not treating or curing myocardial ischemia or another disease or condition. Accordingly, the Examiner's anticipation rejection based on Ning should be reversed. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986) ("It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention.").

Applicants also submit that a PARG inhibitor is not disclosed in Wang or Ning, at least one that is sufficiently described to allow one of skill in the art to think it acts in a therapeutic manner with respect to damaged tissue. The Examiner incorrectly assumes that the ginseng described in Wang and Ning must necessarily contain lignin glycoside (a known PARG inhibitor disclosed in the Tanuma references) and that such lignin glycoside must be present in a therapeutically effective amount. (Action, pg. 3.) Neither Wang nor Ning mention lignin glycoside or any other PARG inhibitor. The Examiner has simply read lignin glycoside into these references because he inherently assumes it must be present in the ginseng. That is a faulty assumption.

There are at least dozens of distinct compounds/agents in any one type of ginseng, and there are many different types of ginseng. Moreover, there is no consensus among those of ordinary skill in the art as to which particular component of ginseng may have a health benefit—if indeed ginseng has any particular health benefit whatsoever. The Examiner's unwarranted reading of this claim limitation (i.e., a PARG inhibitor) into Wang and Ning should be disregarded.

Moreover, the Examiner's contention that "Tanuma teach that ginseng hot water extract contain[s] the lignin glycoside" and therefore reads on the method taught by Wang and Ning is fraught with highly relevant factual inaccuracies. (Action, pg. 3.) Wang, Ning, and Tanuma (both Tanuma AB and AC describe identical procedures for this particular point) teach three entirely different extraction procedures involving ginseng.

The first point to note is that Tanuma does indeed teach that a hot or boiling water extraction is necessary to properly extract the lignin glycoside.[6] (Tanuma AC, Ex. D, pgs. 5-7.) But that is only the first extraction step. Left completely unmentioned by the Examiner is that the boiling water extract is then further extracted with a basic aqueous solution, which is subsequently acidified and diluted with ethanol, whereby a ginseng precipitate is recovered and used as the active agent. (Tanuma AC, Ex. D, pg. 5.) Therefore, if one takes a whole ginseng root, and follows the detailed extraction procedures in Tanuma, lignin glycoside is recovered in presumably relatively pure form for possible therapeutic use.

Wang, on the other hand, describes a procedure wherein only 30% of a ginseng root (head and tail portion only) is extracted with water and concentrated. (Wang, Ex. A., pgs. 2-3.) Contrary to Tanuma, the extraction is not done with boiling water. Wang's non-boiling water

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[6] The only example in Tanuma AB and AC describes the hot water extraction of pine cones—not ginseng—to ultimately provide the desired lignin glycoside. (Tanuma AC, Ex. D, pgs. 6-7.)

extraction is also not followed up with a further basic extraction (and subsequent isolation procedures). Given these extraction discrepancies, there is no reasonably possibility that one of ordinary skill in the art would read Wang to inherently include the lignin glycoside (at least in a therapeutic amount) that is described in Tanuma.

Ning discloses yet another ginseng extraction that is different than Tanuma. Ning tells one of skill in the art to boil (in water) and concentrate 6-16 parts ginseng, 60-100 parts Acanthopanax root or Acanthopanax bark or Acanthopanax, and 10-90 parts pilose antler blood or pilose antler extract.[7] Whereas Tanuma conducts a series of extractions to a boiled extract of 100% ginseng root to provide a relatively pure lignin glycoside PARG inhibitor, Ning simply concentrates (after boiling) this rather exquisite concoction to leave what the Examiner surprisingly assumes is pure lignin glycoside. Obviously the amount of ginseng extract (and to an unknown smaller proportion the purported lignin glycoside) is a small part of this concoction—certainly not of the amount (if any at all) necessary to eventually yield a therapeutically effective concentration of lignin glycoside to be administered as directed in claims 46-49. The Examiner's assumption that the lignin glycoside disclosed in Tanuma is inherently present in Wang and Ning represents clear error and must be disregarded with respect to the anticipatory rejection.

With respect to the Tanuma references, it is not clear from the entirety of the Examiner's comments in the Final Office Action whether either Tanuma reference is being cited as an anticipatory reference or solely used to support his reading of lignin glycoside into Wang and Ning. Both Tanuma references disclose lignin glycoside as a PARG inhibitor. Tanuma AB

[7] Twenty to thirty parts of wolfberry fruit and 600-1000 parts of sugar and a suitable amount of citric acid are added to the aforementioned concentrated extract.

teaches that inhibitory PARG activity is useful for treatment and prevention of malignant tumor (anti-cancer) and viral infection. (Tanuma AB, Ex. C, pgs. 4-5.) Tanuma AC discloses that lignin glycoside used as a PARG inhibitor is useful as an anti-cancer and anti-viral agent, a cytokine intensifying agent, and a cytokine production inducing agent. (Tanuma AC, Ex. D, pgs. 4-5.)

Neither Tanuma reference, however, discloses or suggests using a PARG inhibitor to treat neural or cardiac tissue damage resulting from a disease or condition as in claim 46. And neither Tanuma reference discloses or suggests using a PARG inhibitor to treat neural or cardiac tissue damage resulting ischemia, reperfusion injury, neurodegenerative disease, neurological disease, head trauma, cardiovascular disease, heart attack, and vascular stroke as in claim 47. The Examiner's view is apparently consistent with applicants' position as he has previously noted: "Tanuma do[es] not specifically teach employment of the lignin glycoside for treating disease[s] directly related to the activity of poly(ADP-ribose) polymerase, e.g., cellular energy depletion, apoptosis or neurological disorder." (May 31, 2001 Office Action, Paper no. 22, pg. 4.)

In the Final Office Action the applicants' attention was also directed to In re Swinehart, which was cited to support the Examiner's comment "that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter." Applicants believe the Examiner is focusing on the wrong part of the claims for novelty. Claims 46-49 are not claiming the old "thing" (e.g., lignin glycoside) referred to in In re Swinehart on the basis of newly discovered properties or functions. Rather, applicants are claiming (see, e.g., claim 46) PARG inhibitors that are used in novel methods of treating neural or cardiac tissue damage resulting from a disease or condition. Claims 47-49 exemplify a particular embodiment of the invention

by expressly naming preferred diseases and conditions. Such method claims are well recognized as patentable subject matter. 35 U.S.C. § 100(b); In re Schoenwald, 964 F.2d 1122, 22 U.S.P.Q.2d 1671 (Fed. Cir. 1992); Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 875, 228 U.S.P.Q. 90, 99 (Fed. Cir. 1985) ("Even if a composition is old, a process using a known composition in a new and unobvious way may be patentable.").

B. The Claims are Patentable Over Wang or Ning in View of Tanuma AB or AC

Claims 46-49 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang or Ning in view of Tanuma (AB and AC). (Action, pgs. 3-5.) The Examiner's obviousness rejection has no foundation because (1) there is no objective motivation to combine Wang or Ning with Tanuma, and (2) as primary references, Wang and Ning do not teach or suggest any of the claim elements and their combination with Tanuma leaves one of skill in the art only with the deficient teachings of Tanuma with respect to claims 46-49.

When an obviousness rejection relies on the combination of prior art references, there must be some objective evidence to combine the references to yield the claimed invention. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1999); *see also In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992) (holding the examiner can satisfy the burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"). Accordingly, the Federal Circuit has made clear that it is imperative that the prior art references must teach or suggest the combination of the references to yield the claimed invention. That standard for a viable obviousness rejection has not been and cannot be satisfied here.

There would have been no motivation for one skilled in the art to combine Wang or Ning with Tanuma (AB or AC) to yield the claimed invention. Starting with the primary references (Wang and Ting), as noted earlier, these references teach a health beverage containing either

sugar free or coffee-flavored ginseng tea. Contrary to the Examiner's unfounded conclusions, the consumption of such ginseng teas provides no plausible therapeutic treatment of any underlying health disease or condition. Neither Wang nor Ning teach or suggest a PARG inhibitor of any type. There is also no mention or suggestion of treating neural or cardiac tissue damage in the references. The primary references of Wang and Ning simply do not teach or suggest any of the claim limitations of claims 46-49.

The secondary references cited by the Examiner, Tanuma AB and AC, disclose that PARG inhibitors exist (e.g., lignin glycoside) and are therapeutically useful in mammals as anti-tumor and anti-viral agents. When the references are viewed together, one of ordinary skill in the art is not going to logically expand upon Tanuma's limited therapeutic uses of PARG inhibitors with the teachings of Wang and Ning. There was and still is no objective connection between Tanuma and the Wang and Ning references, even with the impermissible hindsight of applicants' invention. *See C.R. Bard, Inc. v. M3Sys., Inc.*, 48 U.S.P.Q.2d 225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding.").

Even assuming, *arguendo* that the references are properly combined, there is no teaching or suggestion that a PARG inhibitor (e.g., Tanuma references) can be used to treat neural or cardiac tissue damage resulting from a disease or condition in a mammal in need thereof. *See* claim 46. Neither Wang nor Ning plausibly teach or suggest an actual therapeutic treatment of any underlying disease. Thus, while the Tanuma references teach PARG inhibitors, they do not cure the deficiencies of Wang and Ning by disclosing or suggesting the methods of use described in claims 46-49. Indeed, the Examiner has already noted that Tanuma only teaches certain uses of lignin glycoside—uses not directed to the claimed method of treating neural or cardiac tissue

damage resulting from a disease or condition, such as ischemia and reperfusion injury. (See Action, pgs. 3-4).

Applicants respectfully request that the Board reverse this obviousness rejection.

C. Separately Patentable Claims

Claims 48-49 are directed to particular diseases or conditions that a PARG inhibitor will treat if administered to a mammal in need thereof. These claims represent a species of the more generic claims 46-47. As such, applicants believe claims 48-49 are separately patentable from claims 46-47.

IX. Conclusion

For the foregoing reasons, the rejections of Claims 46-49 should be reversed.

Respectfully submitted,

Date: May 10, 2002

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APPENDIX

46. A method of treating neural or cardiac tissue damage resulting from a disease or condition in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of an inhibitor of poly(ADP-ribose) glycohydrolase.

47. The method of claim 46, wherein the disease or condition is ischemia, reperfusion injury, neurodegenerative disease, neurological disease, head trauma, cardiovascular disease, heart attack, and vascular stroke.

48. The method of claim 47, wherein the disease or condition is ischemia.

49. The method of claim 47, wherein the disease or condition is reperfusion injury.